Idiopathic Hemochromatosis: Serum Ferritin Concentrations during Therapy by Phlebotomy

Phillip J. Garry¹ and John H. Salki²

We report the case of a 54-year-old man who presented with symptoms of idiopathic hemochromatosis, an inherited disorder involving regulation of iron absorption. These symptoms usually do not appear until total body iron content reaches 15 g, about threefold normal. Therapy involves mobilization and removal of excess stored iron through weekly or twice-weekly phlebotomies of 500 mL, until the hemoglobin concentration becomes <110 g/L and remains there for several weeks, or until serum ferritin concentrations indicate that almost all the stored iron has been removed (ferritin <12 µg/L). Here, concentrations of ferritin in serum were used as an index to iron overload and removal of stored iron. We report changes in hemoglobin, serum ferritin, iron, and total iron-binding capacity during the course of removing by phlebotomy more than 20 g of iron from a patient with idiopathic hemochromatosis.

Additional Keyphrases: iron, hemoglobin, total iron-binding capacity, heritable disorders, screening, monitoring therapy

To confirm a diagnosis of suspected idiopathic hemochromatosis in a patient who presents with any or all of the classical symptoms—unexplained hepatomegaly, liver disease, unusual skin pigmentation, diabetes, arthritis, loss of libido, and idiopathic cardiomyopathy—it is necessary to determine if the patient in fact has excessive body stores of iron. In clinical practice, information on the serum iron concentration, the percentage transferrin saturation, and the serum ferritin concentration provide the best index such.

The serum iron concentration in idiopathic hemochromatosis is usually in the high-normal or above-normal range. Total iron-binding capacity (TIBC) is usually less than normal, perhaps because of diminished transferrin synthesis as a result of iron overload and associated liver disease (1). Consequently, the transferrin saturation ranges from 80 to 96%. In untreated patients with idiopathic hemochromatosis, the serum ferritin is five- to 50-fold normal (500 to 5000 µg/L); recent evidence indicates that serum ferritin concentration and the concentration of iron in liver tissue are well correlated (2, 3).

Measurements of serum ferritin are also helpful in screening family members of affected subjects, in whom iron stores may be increased but not to toxic concentrations. However, serum ferritin is also increased in patients with inflammatory diseases, acute liver damage, and various carcinomas (4-6). A liver biopsy revealing large parenchymal deposits of iron is the definitive finding for the diagnosis of idiopathic hemochromatosis, so this procedure is usually recommended if results of any of the preceding tests are abnormal (7). Another measure of parenchymal iron is the amount of iron excreted in the urine during the 24 h immediately after intramuscular injection of 10 mg of the chelating agent desferrioxamine per kilogram of body weight; normally, less than 2 mg of iron is excreted, but in idiopathic hemochromatosis the amount is usually 4 mg or more (8).

Case Report

In March 1979, a 54-year-old man was referred by his personal physician to this institution for further evaluation of suspected idiopathic hemochromatosis.

In June 1977, about a year after becoming manager of a meat-packing company, he had begun to feel lethargic, weak, and in generally poor health. At this time he was hospitalized for three weeks and found to have severe upper gastrointestinal bleeding, believed to be from a duodenal ulcer. He also had a recurrent fever of unknown etiology, which was later presumed to be caused by a brucella infection, because he had a positive antibody response to brucella. He was subsequently treated with tetracycline for three weeks for the brucella infection but did not regain his former state of health.

In December 1977, the patient was thought to have a possible re-exacerbation of his brucellosis and was placed on a four-week course of treatment with tetracycline.

In January 1978, a liver-spleen scan revealed hepatosplenomegaly, and liver-function tests revealed hypoalbuminemia, prolonged prothrombin time, slightly increased activities of aspartate and alanine aminotransferases, and hyperbilirubinemia.

A liver biopsy done in February 1978 showed fine micronodular cirrhosis with massive iron retention. The histological appearance was consistent with the diagnosis of hemochromatosis, but was thought not to correlate with the patient's clinical presentation at that time. Because of problems with accumulation of fluid, the patient was placed on a regimen of diuretics and a restricted sodium diet.

In May 1978, he was admitted to a local hospital because of marked ascites and abdominal pain. He was treated for these problems and discharged to continue under the care of his private physician.

In January 1979, the patient was re-evaluated by his local physician and the following laboratory results were recorded. Tests for hepatitis antibody in the serum gave negative results. His serum albumin concentration was 26 g/L and activities of the serum aminotransferases were above normal. His serum iron and TIBC concentrations were 1280 and 2500 µg/L, respectively. Three months previously (October 1978) the patient's serum iron and TIBC concentrations were 730 and 1980.

¹ Department of Pathology and Clinical Nutrition Laboratory, and
² Department of Medicine, University of New Mexico School of Medicine, Surge Bldg. Room 236, Albuquerque, NM 87131.

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µg/L, respectively. Two weeks before being referred to this institution (March 1979), a bone-marrow aspirate showed markedly increased reticulendothelial iron, and a skin biopsy showed iron in the endothelial cells of the blood vessels and dermal collagen. There was also increased melanin pigment in the basal cell layer, another manifestation of hemochromatosis. Serum ferritin concentration was 2825 µg/L. A glucose-tolerance test revealed a diabetic pattern; the glucose concentration in serum during fasting was 1.71 g/L. The patient was diagnosed as having the adult-onset type of diabetes, and subsequently he was placed on insulin therapy. After injection of desferrioxamine, 15 mg of iron was excreted in the urine in 24 h.

The patient had no history of hepatitis or excessive alcohol intake. He had been diagnosed as having sarcoidosis in 1972, for which he was treated with steroids for several months. There were no serious childhood illnesses. Surgery included tonsillectomy, appendectomy, herniorrhaphy, and hemorrhoidectomy. Both parents died of myocardial infarctions, the father at 72 and the mother at 79 years of age.

When the patient was referred here in March 1979 for treatment of suspected idiopathic hemochromatosis, his weight had been relatively stable for several months, but his weight had declined by about 18 kg in less than two years.

Methods

Blood was collected by venipuncture before each phlebotomy treatment. Hemoglobin was determined by the cyanmethemoglobin method, serum ferritin by the noncommercial radioimmunoassay method of Miles et al. (9). Serum iron and TIBC were measured by automated colorimetry (10). The mean (and 2 SD) normal values for these measurements in our laboratory, as determined from specimens from 25 healthy first-time male blood donors, are as follows: hemoglobin, 157 (19) g/L; serum iron, 900 (500) µg/L; TIBC, 3540 (1020) µg/L; and percent transferrin saturation, 24.5 (14.6) percent. The mean for serum ferritin was 93 µg/L, the values ranging from 34 µg/L to 281 µg/L for these persons.

After each phlebotomy, the volume of blood removed was recorded and— together with the hemoglobin concentration and a value of 3.4 mg of iron per g of hemoglobin—used to calculate the amount of iron removed.

Results

When the patient began phlebotomy therapy for hemochromatosis in March 1979, his initial serum ferritin concentration was 2825 µg/L. After 13 phlebotomies we decided that all laboratory measurements for iron would be performed at each phlebotomy. Thus the first recorded values for all laboratory assays began with the fourteenth phlebotomy (April 23, 1979). In all, 109 phlebotomies were performed during a 17-month period. At the fourteenth phlebotomy, the laboratory results were: ferritin, 1825 µg/L; iron, 1370 µg/L; TIBC, 1580 µg/L; and calculated transferrin saturation, 87% (see Figure 1). When the ferritin concentration reached 12 µg/L, we assumed that most of the iron reserves had been mobilized and that the patient's iron stores were nearly exhausted. At that time, the total amount of iron removed during the 109 phlebotomies was calculated to be 20 g, and the amount of iron remaining after each individual phlebotomy was subtracted from this value. These amounts are recorded on the abscissa of Figure 1 vs the laboratory results on the ordinate.

Several interesting observations can be noted from Figure 1. The ferritin values declined, although fluctuating quite dramatically, during removal of the first 9 g of iron. Thereafter they remained relatively constant—between 500 and 700 µg/L—as the next 4 g of iron was removed. Then the steady drop was resumed until the ferritin concentration reached 12 µg/L. A regression analysis of ferritin concentration vs total iron remaining showed that each microgram per liter decline in ferritin represented 11 mg of storage iron. This value is very similar to reported values, even though there were substantial ferritin fluctuations and hesitations during the course of the phlebotomies (11).

Serum iron values fluctuated over a fairly narrow range, 1350 to 1850 µg/L, until about 5 g of storage iron remained. Then the substantial and rapid decline in serum iron paralleled the diminutions in ferritin and hemoglobin, and was accompanied by steady increases in TIBC. TIBC values remained quite low (approximately 1600 µg/L) during the period when storage iron went from 20 to 15 g. During removal of the next 10 g of iron, TIBC values increased to between 2000 and 2300 µg/L, remained at this higher level for a considerable time, and then dropped below 2000 µg/L when 7 g of iron remained. During removal of the last 5 g of iron, TIBC concentrations began to rise steadily but never reached 3000 µg/L.

Calculated values for percent saturation of transferrin remained in the range of 70 to 95% until approximately 15 g of iron had been removed, then steadily declined to 7% as the storage iron neared exhaustion.

Hemoglobin values remained in the 110 to 127 g/L range during the removal of the first 9 g of iron and then increased, staying at 130 g/L or more until about 5 g of iron remained. Then, as mentioned previously, hemoglobin values dropped steadily and a final value of 93 g/L was recorded at the termination of the study.

The patient continues to be followed regularly for evaluation and has phlebotomies at two-month intervals. Results of liver-function tests are now normal, but control of his diabetes continues to require exogenous insulin. He has gained about 8 kg during the three years of treatment, with improved strength and feeling of well-being.

![Figure 1](image-url)
Discussion

This patient presented with many of the classical symptoms of idiopathic hemochromatosis: weakness, lassitude, changes in skin pigmentation, diabetes, weight loss, abdominal pain, hepatosplenomegaly, and ascites. Liver biopsy revealed increased periportal iron and cirrhosis; bone-marrow aspirate revealed increased reticuloendothelial iron. The urinary excretion of iron after an intramuscular injection of desferrioxamine was also consistent with excessive iron storage. The serum ferritin concentration (2825 μg/L) just before therapy with phlebotomy was consistent with the results of liver biopsy, bone marrow, and chelation evaluations for iron overload.

Were all of these laboratory tests necessary for positive identification of an iron overload condition? In this individual, the serum ferritin value indicated increased iron stores, and other conditions in which serum ferritin is increased in the absence of iron overload—such as acute liver damage, chronic infection, and carcinomas—were not present. Therefore, the serum ferritin value and liver biopsy results should have sufficed, along with other clinical findings, to assure the diagnosis. Some confusion might have arisen in the interpretation of the serum iron (730 and 1260 μg/L) and TIBC value (1980 and 2500 μg/L) six and three months, respectively, before the phlebotomies were started. These values correspond to 37% and 50% saturation of transferrin, which is not consistent with values ordinarily found in individuals with idiopathic hemochromatosis; however, a few cases of marked iron overload, in which the percent saturation of transferrin was not increased, have been cited before (1). Considering the initial series of increased values for percent transferrin saturation during therapy, the corresponding low (26 g/L) albumin concentration, and the abnormally high ferritin concentration (2825 μg/L) before phlebotomy was begun, we can only conclude that the pre-phlebotomy serum iron or TIBC determinations, or both, recorded three and six months before phlebotomy was begun were possibly in error or that this case does not fit the typical serum iron and TIBC patterns usually noted in individuals with idiopathic hemochromatosis (7, 12).

Our results (Figure 1) demonstrate, as others have shown, that values for ferritin do not decrease in a completely linear fashion as the iron load decreases (13).

Figure 1 also shows that individuals with a serum ferritin near 500 μg/L can be suspected of having increased iron stores if one can rule out other conditions that cause serum ferritin to increase, such as inflammatory diseases, acute liver damage, and various carcinomas.

Serum iron values were within the normal range when this patient was undergoing phlebotomy. The reason for this finding is probably related to the low TIBC values, which in turn probably reflect diminished transferrin synthesis resulting from iron overload and the patients' cirrhotic liver. We did not perform liver-function tests at intervals during therapy, so this is only a speculation. However, during the later stages of therapy, the transferrin concentration increased, as demonstrated by the steady increase in TIBC values with a subsequent decrease in iron and percent transferrin saturation values. This finding is consistent with removal of the toxic iron load from the liver and a subsequent return of the liver's ability to synthesize transferrin.

The information presented here represents only one case study of a patient with idiopathic hemochromatosis, but the laboratory test results during the therapy by phlebotomy should be useful for clinicians dealing with similar cases of this rare problem. It also underscores the usefulness of measuring serum ferritin during the initial screening process and in following the course of therapy.

References